- constituted or terminated respectively by A units of glucosamine structure, in particular D-glucosamine, and U units of glucuronic acid structure, in particular D-glucuronic, or iduronic acid, in particular L-iduronic acid;

- one of the units A or U being an alcohol in which the -OH group of the alcohol function occupies any one of the positions 3, 4 or 6 in the case of unit A and 2, 3 or 4 in the case of unit U, the other unit possessing an activated anomeric carbon, that is to say comprising a reactive group capable of establishing with the -OH group of the alcohol the desired glycosylation -O- linkage, in the desired stereochemistry, to form a -A-U or -U-A sequence;

the reactive group of A and U being compatible with the protective and/or functional groups present on the units;

all the position of A and U excepted those of which the anomeric carbon is activated bearing -OH, amino or carboxyl groups, or precursors of such groups, the groups themselves, when they are present being blocked by one or advantageously several types of protective groups, these various groups being compatible with one another and with the above precursors, these protective groups and precursors being inert with respect to the glycosylation reaction and with the reactive groups, permitting the positioning, in the course of subsequent operations, of given substituents at the various positions, and this, as the case may be, sequentially, the conditions of application to cause the starting substances to react being

selected so as to retain the structure of the units of these substances and the nature of the various substituents present, provided that the establishment of the interglucoside linkage does not lead to the production of a disaccharide with a [2-N-sulfate or(2-N-acetyl)-6-O-sulphate-D-glucosamine] -[methyl-D-glucuronic acid] structure.

6. A process according to claim 5, wherein the A and U units of the sequence formed include temporary protective groups, wherein the groups are capable of selectively blocking a position of the A or U unit intended to take part in a novel glycosylation reaction, these groups being removable in the presence of the other groups present on the units of the starting products to recreate an alcohol.

7. A process according to claim 5, wherein the developed oligosaccharide chain is subject to one or several chemical reactions in order to introduce a given type of functional group or, successively several types of groups, then to form, if desired, derivatives of these functional groups.

8. A process according to claim 7, wherein the functionalization step is effected by eliminating only a part of the protective groups and /or certain precursor groups of the amino derivatives or again the whole of the protective groups and/or of the precursor groups and by introducing in their place a given type of substituent of successively different substituents, then by releasing a portion or all of the -OH groups still blocked, if desired.

9. A process according to claim 5, wherein the starting materials contain several types of protective groups, namely (1) one or several semi-permanent groups, i.e. a group removable in the first place after the reactions of glycosylation when the saccharide skeleton includes the number of desired units, without removal or alteration of the other groups present, and (2) one or several permanent groups, i.e. groups capable of maintaining the protection of the -OH radicals during the introduction of the functional groups in place of the semi-permanent groups, said protective group being such as acyl, alkyl possibly substituted or aryl radicals.

10. A process according to claim 5, wherein A comprises at the 2 position a nitrogen group advantageously constituted by groups such as $-N_3$ or $-NHCOO-CH_2C_6H_5$, or any other group constituting a precursor of the amine function or of an amine derivative, in particular $-NHSO_3^-$ or -NH-acyl, more especially $-NH-COCH_3$.

11. A process according to claim 5, wherein the carboxyl functions of the U units, are blocked by groups inert with respect to reactions used for the replacement of the protective groups and removal at the end of the synthesis to liberate the carboxyle groups, possibly for the purposes of salt formation, these protective group of carboxyl function being selected advantageously from among alkyl radicals or aryl radicals.

12. A process according to claim 6, wherein for a U-A disaccharide lengthening towards the left, the temporary group is present on the U unit and for lengthening to the right on the A unit, enabling the obtention as desired, by successively carrying out glycosylation reaction of enchainment $U_wA_xU_yA_z$ in which the sum of the indices is comprised between 2 and 12, these values being included in the range, where w and y cannot be nil simultaneously, regular enchainments being of the type $U(AU)_n$, $(AU)_nA$, $(UA)_n$ or again $(AU)_n$ with n equal to 1 to 6.

a'

13. A process according to claim 12, comprising the use in place of one or several A or U units, a structural analog of an A or U unit, such as a neutral sugar or a desoxy-sugar, or other uronic acid units or amino sugars U or A of different configurations.

14. A process acccording to claim 5 wherein the above alcohol is reacted with a reactive derivative such as a halide, advantageously a chloride or a bromide, an imidate or an orthoester,

-the condensation reaction between the halide and the alcohol being advantageously of the Koenigs-Knorr type and carried out in a solvent medium, more especially in an organic solvent, particularly of the dichloromethane or dichloroethane type, advantageously in the presence of a catalyst generally a silver or mercury salt, for example, silver trifuloromethane sulphonate, commonly called silver triflate,

silver carbonate, silver oxide, mercuric bromide or mercuric cyanide, and also with a proton acceptor such as sym-collidine and an extractor for the water possibly present and/or for the halohydric acid formed, for example 4 A molecular sieves, at room temperature or again at a lower temperature which can reach $0^{o}C$ or less, in an atmosphere of an inert gas such as nitrogen or argon, or alternatively for forming covalent bonds between alcohols of various structures and an L-idose precursor of the L-iduronic acid, the condensation reaction is carried out by using as catalyst mercuric derivatives, in particular cyanide and/or mercuric bromide, molecular sieves parricularly 4 A molecular sieves, in an organic solvent selected according to the reactivity of the alcohol,

a'

-the condensation with an orthoester such as a 1,2-O-methoxy-ethylidene group being preferably carried out at a temperature above $100^{o}C$ in a solvent medium of the chlorobenzene type or any other solvent whose boiling point exceeds 100^{o} and is advantageously between 100 and $150^{o}C$ in the presence of a catalyst such as 2,6-dimethyl pyridinium perchlorate,

-the condensation with an imidate being carried out at low temperature, more especially at a temperature below or equal to about $0^{o}C$, in a solvent medium, such as dichloromethane, in the presence of a 4 A molecular sieve and a catalyst such as boron trifluoride etherate.

15. The process according to claim 6, wherein the alcohol function of one of the units A or U involved in the saccharide sequence already formed is advantageously liberated from its temporary protective group, for example

from an allyl group, by a treatment such as one comprising first the use of an isomerifing agent such as Pd, Rh and Ir derivatives, in particular rhodium tris-triphenyl-phosphine chloride (I), or again potassium tertio-butoxide, then under acid conditions, in particular with a mixture of mercuric oxide and mercuric chloride, or by saponification from an -O-acyl group, in particular -O-acetyl or -O-chloracetyl, these radicals being removable, for example, by means of thiourea in a solvent medium, advantageously at a temperature higher than 80°C, preferably of the order of 100°C.

16. The process according to claim 6, wherein the OH radical protective groups, apart from the temporary groups already considered, are selected from the group comprising acyl radicals (particularly acetyl, alkyl, substituted alkyl such as benzyl), and for two neighboring positions, among the acetal groups of ketals, for example benzylidene, other forms of protection consisting of the blocking of two -OH groups in an epoxide form or of a 1,6-anhydro bridge.

17. The process according to claim 6, wherein the products used in the glycosylation reactions contain several types of protective groups, which permit in the course of the

step of functionalization the successive introduction of one or several functional groups and the liberation of one or several -OH radicals if desired, the protective groups may already be occupying certain positions on the products applied in the glycosylation reaction or alternatively being introduced from other groups once the saccharide skeleton is formed, this modification comprising, for example, the use for glycosylation of a substance A in which the -OH groups at the 2 and 3 positions and at the 1 and 6 positions are blocked in anhydrous form, respectively 2,3-expoxide and 1,6-anhydro, the opening of the epoxide function by the sodium azide enabling the introduction, at the 2 position, of an N_3 group which hence constitutes a precursor of an amine function.

a'

18. A process according to claim 5, wherein the -OH radicals of the starting materials intended to be sulfated are protected by acyl groups, in particular acetyl, while the -OH radicals intended to be liberated at the end of the synthesis are protected by a permanent group such as the benzyl group.

19. A process according to claim 5, wherein the whole saccharide chain formed is subjected to a given chemical reaction in order to introduce a particular type of substituent, for example, to an esterification, particularly a sulfation by means of a suitable agent, carried out under conditions not changing the oside structure, this sulfation being carried specifically or not, as necessary on the fully protected glycoside.

20. A process according to claim 5, wherein the functionalization step is effected selectively so as to introduce on the chain, successively, several types of substituents, particularly the sulfate group on the predetermined position of the units, to form at the 2 position of the A units an amino derivative and in the 6 position of U units, an acid derivative, and to free the -OH radicals at other positions, said functionalization step being carried out by using derivatives in which the semi-permanent groups occupying positions intended to be sulfated are constitued by -O-acetyl groups, the positions corresponding to an -OH group intended to be liberated, being occupied by semi-permanent groups constituted by benzyl groups, the 2 positions of the A units being substituted by groups such as N_3 or NH-COO- CH_2-C_6H_5 and the 6 positions of the U units being occupied by carboxyl groups protected by an alkyl radical, in particular methyl.

a'

21. The process according to claim 20, wherein the functionalization step comprises

-the selective introduction of the sulfate groups after having eliminated the -O-acetyl blocking group by a saponification reaction carried out by means of a strong base such as soda, preferably at a temperature below ambient temperature and more especially close to $0^{\circ}C$, the product resulting from the hydrolysis being then subjected to the action of an alkylation agent in order to introduce, on the carboxyl group, the protected alkyl groups which are found to

be removed on hydrolysis, said alkylation being followed by a sulfation treatment to introduce sulfate groups at the positions released by hydrolysis and left free after the action of the alkylation agent, said sulfation comprising the utilization of a sulfation agent, such as a trimethyl--amine/SO_3-complex, in a solvent medium, more especially in a solvent such as dimethylformamide, preferably at a temperature higher than room temperature, generally in the vicinity of 50°C, which corresponds to a reaction time of about 12 hours,

a'

-the liberation of the -OH groups blocked by the benzyl radicals, by removal of the benzyl groups, by catalytic hydrogenation under conditions compatible with the maintenance of the sulfate groups and the conversion of the nitrogenous groups into amino functional groups, preferably under hydrogen pressure in the presence of a catalyst of the Pd/C type, in an organic solvent medium, in particular alcoholic, with water,

-the formation of N-acetyl group by submitting the product resulting from the hydrogenation reaction to an acetylation agent such as acetic anhydride, the reaction being advantageously carried out at a basic pH, in particular close to 8 in an aqueous medium, or of N-sulfate group by means of a sulfation agent of the above-indicated type, at a pH higher than 9, advantageously of the order of 9-10,

-the liberation of the carboxyl group by addition of a strong base,

-the salification of the carboxyl group by using for example exchange resins with the desired cation, particularly with sodium, potassium, lithium, magnesium, calcium.

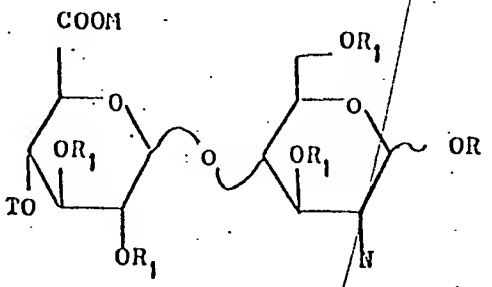
22. The oligosaccharides constituting intermediates in the process according to claim 5.

23. Oligosaccharides according to claim 22 comprising a chain based on binary units of structure $(A-U)_n$ or $(U-A)_n$ corresponding to enchainments a-b or a-c, (or the reverse) in which n is a number from 1 to 6, and binary unit being completely protected and possessing either a reactive group on the anomeric carbon of the unit at the reducing end; or a single free -OH group on the unit at the non-reducing end, this -OH group occupying the 3, 4 or 6 position in the case of an A unit and the 2, 3 or 4 positions in the case of U units, or (2) being constituted by completely protected units such as obtained at the end of the glycosylation step, or (3) comprising products in which one or several -OH groups are liberated, said intermediate oligosaccharides optionally containing one or several consective a or b or again c units and/or one or several units of neutral sugars and/or several dexoxy-sugars in their structure.

a'

24. Olgosaccharides according to claim 23 possessing the structure of heparin or heparane sulfate gragments comprising a 1 $\xrightarrow{\alpha}$ 4a, a $\xrightarrow{\alpha}$ 4b, a 1 $\xrightarrow{\alpha}$ 4c, and b 1 $\xrightarrow{\beta}$ 4a linkages.

25. Olgosaccharides including at least one unit having a structure of the type b 1 $\xrightarrow{\beta}$ 4a of the formula I



(I)

a'

in which:

the R_1 radicals, identical or different from one another, if necessary conjointly with R, represent a protective group, in particular a sp semi-permanent group or a p permanent group,

T, is a temporary group t, or a permanent group p, or a hydrogen atom,

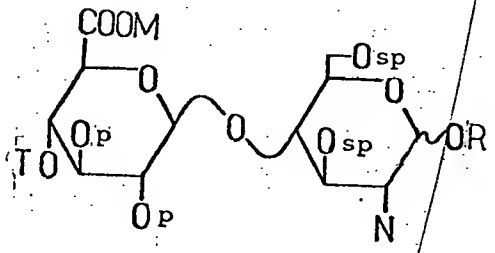
-N, is a nitrogenous group amine or amine derivative precursor.

-R, is an aliphatic or aromatic radical, particularly an alkyl radical comprising from 1 to 4 carbon atoms, where OR represents a reactive group such as a halide or again R an alkyl radical and

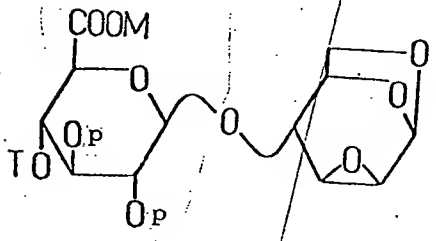
-M, a group blocking the acid function, these various symbols having the above-given meanings

and preferably of the formulae (II), (III), or (IV):

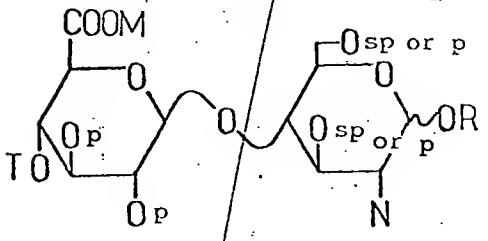
a'



(II)



(III)



(IV)

in which the various symbols have the above-indicated meanings, the symbols given in the formulae (II) to (IV), having independently, or in combination, the following meanings:

-M represents a hydrogen atom or an alkyl radical, particularly methyl,

-sp an acyl group, in particular acetyl,

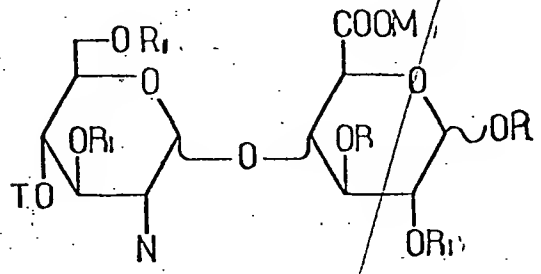
p, a substituted alkyl group, in particular benzyl,

-R, an acyl group at or in particular an acetyl group, an alkyl radical, in particular methyl or substituted alkyl, particularly benzyl, or -OR a halogen, in particular a bromide, or again an imidoyl radical.

-N, an azide group,

-T, the group t representing an acyl radical, in particular acetyl, a halogenated acyl radical, in particular a monochloro or trichloroacetyl radical, or the group p representing a substituted alkyl radical in particular the benzyl radical, as the case may be itself paramethoxy or again a hydrogen atom in order of chain formation of said units being optionally reversed.

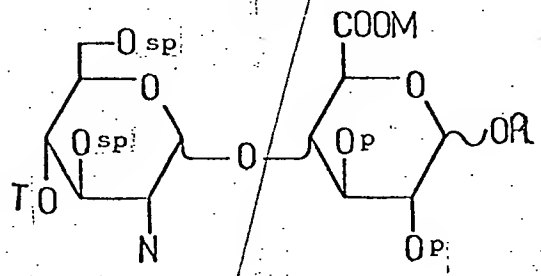
26. Oligosaccharides including at least one unit having a structure of type a 1 ⟶ 4 b of the formulae(V)



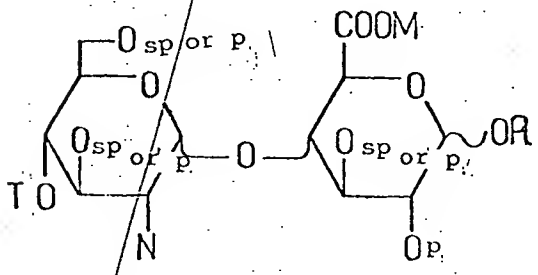
(V)

and preferably of formulae (VI) or (VII)

a'



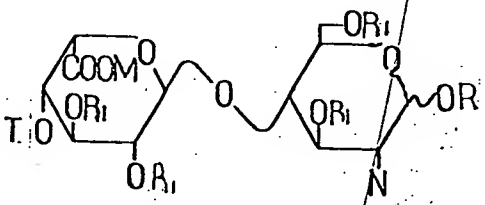
(VI)



(VII)

in which the various symbols have preferably the particular meanings given above with respect to formulae (II) to (IV), R representing in formulae VI or VII, in addition, preferably, a propenyl, allyl, imidoyl, or -H group, with N representing then more especially a -HN-acetyl group.

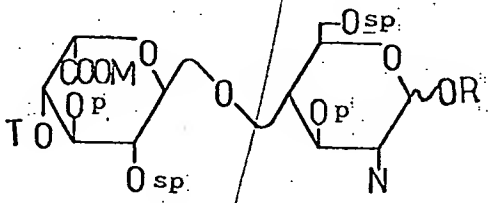
27. Oligosaccharides according to claim 24 including at least one unit having a structure of the type c 1 $\xrightarrow{\alpha}$ 4 a of the formulae (VIII)



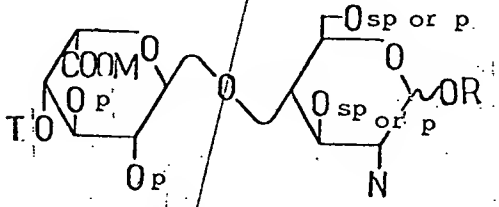
(VIII)

in which the substituents have the meanings given with respect to formula (I) and preferably of the formulae (IX) and (X)

a'



(IX)



(X)

in which

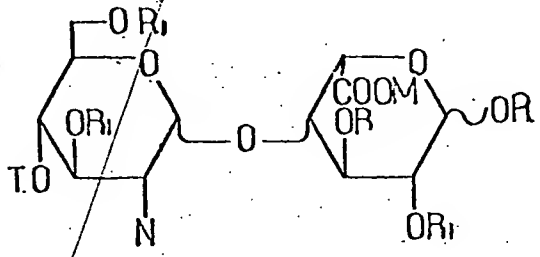
the various sp and p groups may be identical and represent an acyl radical, in particular acetyl, or different, as selected from among acyl radicals, in particular acetyl or benzoyl and aryl or substituted alkyl radicals,

N represents a precursor nitrogen group, possibly different from that present in compounds of formulae (I) to (V), in particular a NHCOO-(substituted alkyl group), particularly a-NH-COO-CH_2-C_6H_5 group, which permits subjecting the nitrogenous groups to different treatments and to form different amino derivatives at 2 position of the A units,

T represents the acetyl, halogenated acyl radical, in particular, monochloro or trichloroacetyl, p-methoxybenzoyl, the symbo,s p, M and R having advantageously the preferred meanings given above in respect to the formulae (II) to (IV).

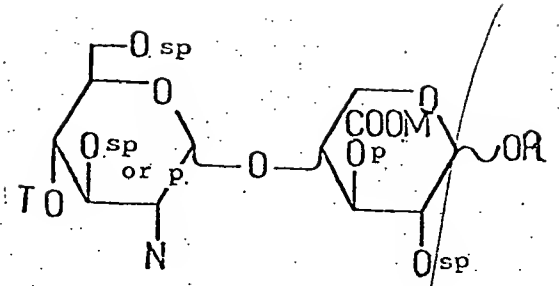
a'

28. Oligosaccharides according to claim 24 including at least one unit having a structure of the type a 1 $\xrightarrow{\alpha}$ 4 d of formulae (XI)

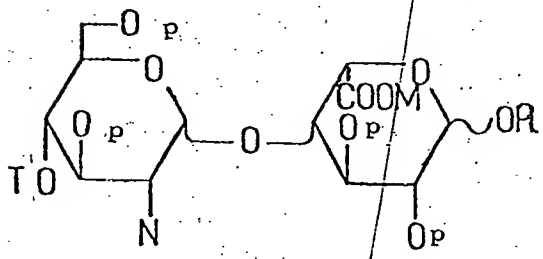


(XI)

in which the substituents have the meanings given above with respect to formulae I, and preferably of formulae (XII) or (XIII):



(XII)



(XIII)

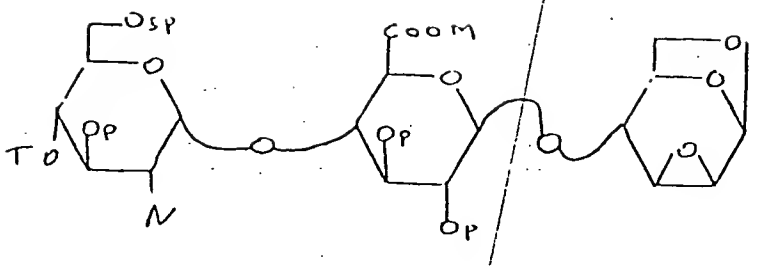
a'

in which the preferred meanings correspond to those given above for formulae (II) to (IV).

29. Intermediate oligosaccharides according to claim 25, corresponding to the products from which the protective groups have been partially removed in the course of synthesis, said products including in particular -OH groups in place of the sp groups.

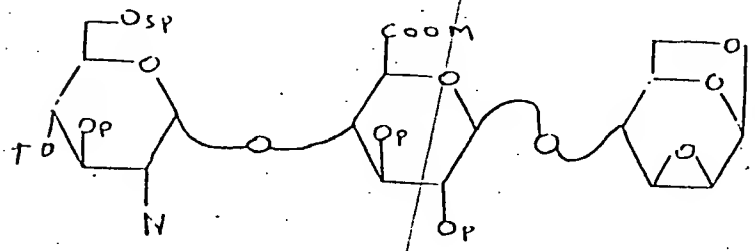
30. Intermediate products corresponding to oligosaccharides containing structures of ABCDEFG, C'DEFGH, AG, BC, CD etc..., ABC, BCD..., ABCD, BCDE..., ABCDE..., ABCDEF, AbCDEF, ABCDEFG or BCDEFGH, perferably

-a trisaccharidic structure more especially a DEF structure corresponding to one of the formulae (XVIII) to (XXI):

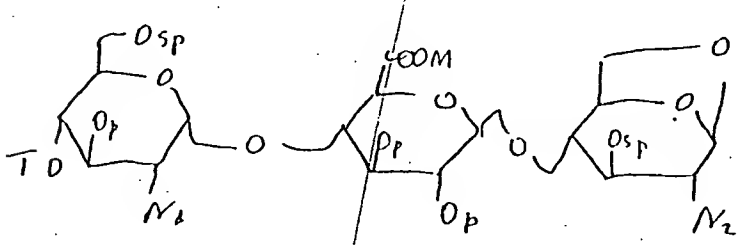


(XVIII)

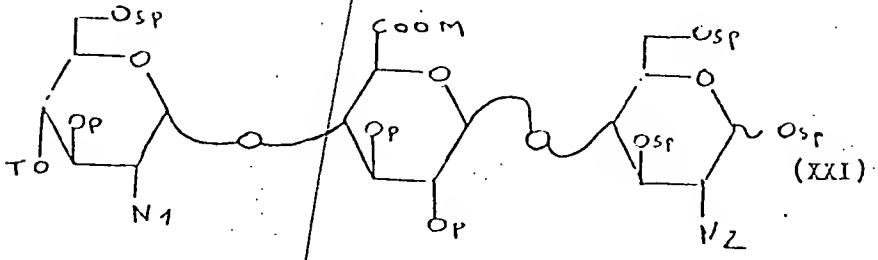
a'



(XIX)

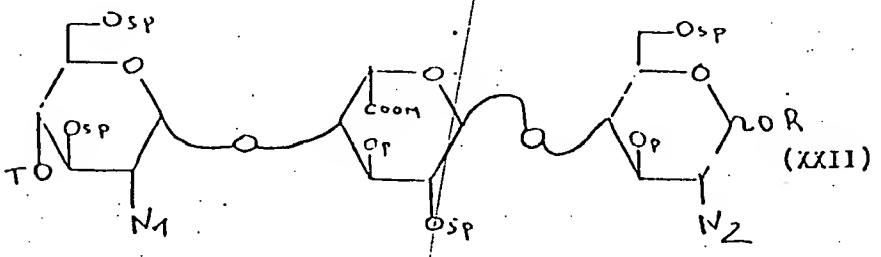


(XX)



(XXI)

in which the substituents have the above mentioned meaning, N_1 and N_2 being preferably identical or different from one another and representing an azide or -NH-acyl group in particular -NH-acetyl, or a structure of the type FGH of formula

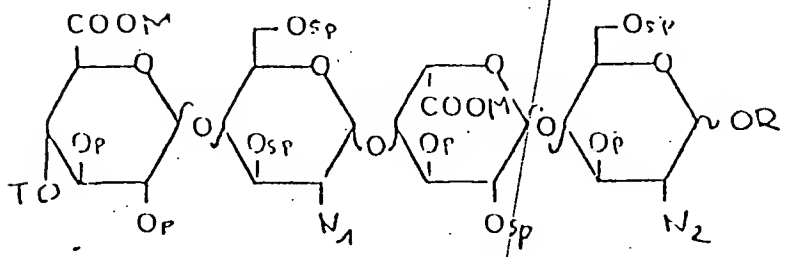


(XXII)

a'

in which the various symbols have the above-given meanings, the two substituents N_1 and N_2 of the two glucosamine units of structure F and H being identical or again advantageously different, as in the case of natural products, and selected from among the azide or -NH-COO-acyl group, in particular -NH-COO-acetyl or -NH-COO-CH_2-C_6H_5,

-a tetrasaccharidic structure, particularly the structure EFGH, corresponding to the following formula

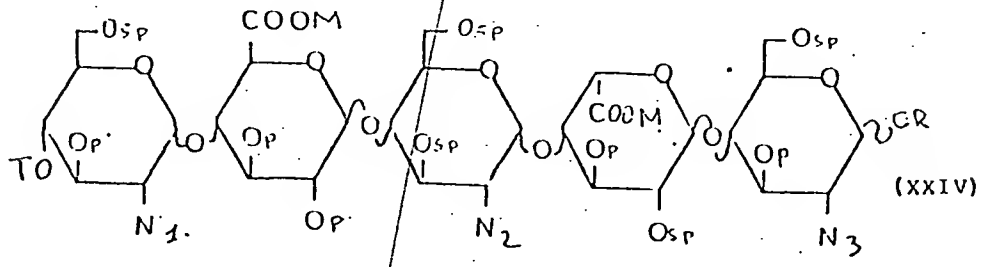


(XXIII)

in which the preferred meanings of the different symbols corresponds to those indicated for formula XXII,

a'

-a pentasaccharidic structure, particularly of the type DEFGH of formula



(XXIV)

in which the various symbols have the above-preferred meanings, and N_1, N_2, N_3 can be identical or different from one another selected from among the meanings already given.

31. Oligosaccharides corresponding to the products according to claim 25,26,27,28, or 29 but in which one, several or all the -OH groups are liberated in the course of synthesis and/or including one or several functional groups, with the exclusion of the disaccharide [2-N-sulfate (or 2-acetyl)-6-O-sulfate-D-glucosamine]-methyl-D-glucuronic acid, said functional groups being constituted preferably by esters and occurring more especially in the form of inorganic anions, particularly be sulfate esters or phosphate esters, these functional groups being borne by one or several primary alcohol and/or seconday alcohol and/or primary amine functions.

a'

32. Oligosaccharides including

-a units substituted at the 6 and/or 3 positions by esters, advantageously in the form of salt with an inorgainc or organic cation, in particular a metal cation, particularly an alkali cation especially sodium, or again a cation derived from a nitrogenous organic base, for example triethylammonium, said a units having also preferably at the 2 position primary amino functional group, advantageously substituted by a group such as sulfate or an acyl group, particularly an acetyl group, and, further including preferably

-units b or c with carboxyl groups free or in the form of salt with an organic or inorganic cation such as defined above, or again protected as above mentioned, and more preferably including units c comprising a sulfate group at the 2 position and/or sulfate groups on the b units, the hydroxyl

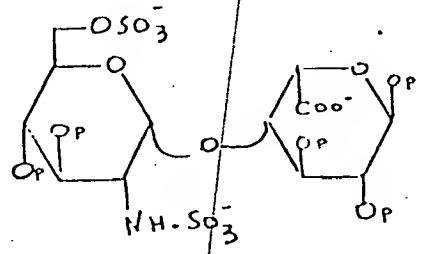
functions of the pyran rings of said units a, b or c being either free, or protected by permanent groups of the alkyl type, in particular by methyl groups.

33. Oligosaccharides corresponding to the products of formulae (I) to (XIII) and (XVIII) to (XXIV) but in which the -sp groups are replaced by anions, and preferably including NHacyl groups, in particular $-NHCOCH_3$, or $NHSO_3$ groups on the a units.

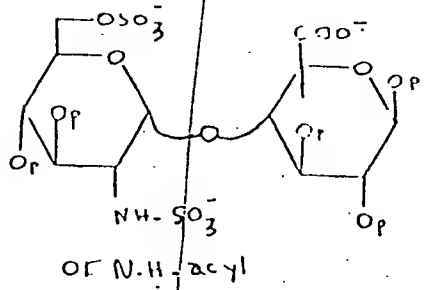
a'

34. Oligosaccharides according to claim 33 including

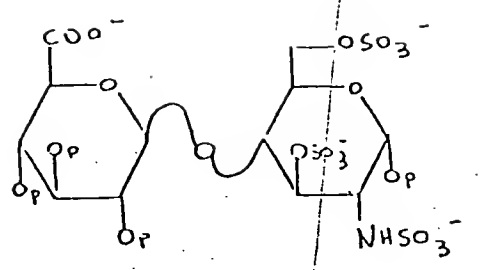
-a disaccharide chain having a structure of the type BD, DE, EF, or GH and corresponding respectively to the following formulae (XXV to XXVIII):



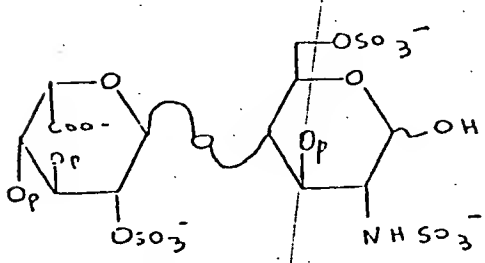
(XXV)



(XXVI)



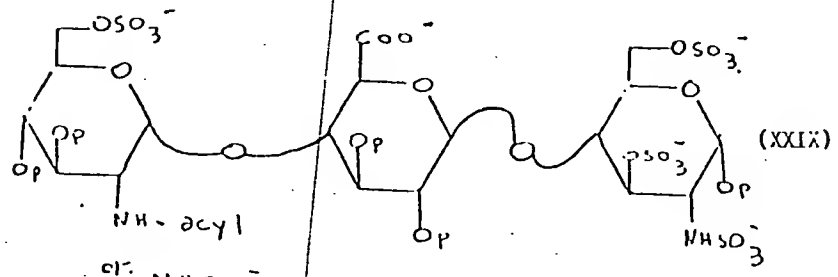
(XXVII)



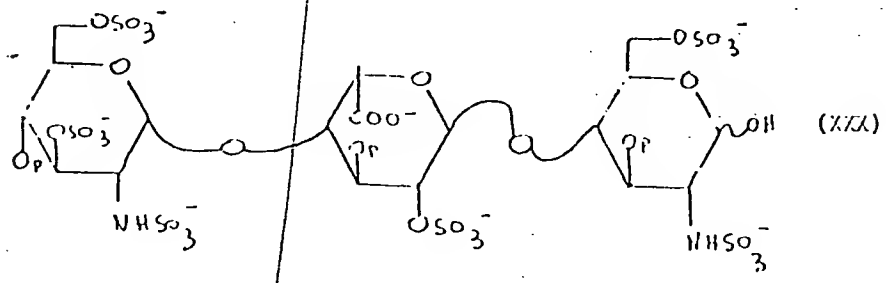
(XXVIII)

a'

-a trisaccharide chain of the structure DEF or FGH respectively or the following formulae (XXIX) and (XXX):

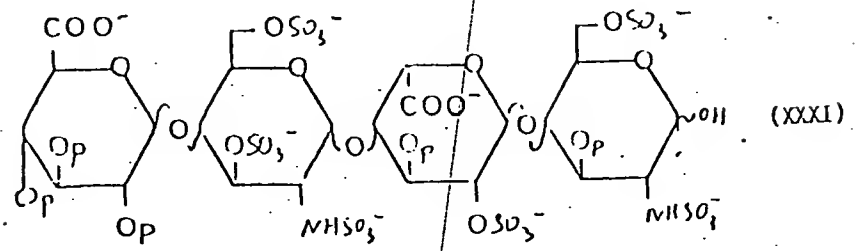


(XXIX)



(XXX)

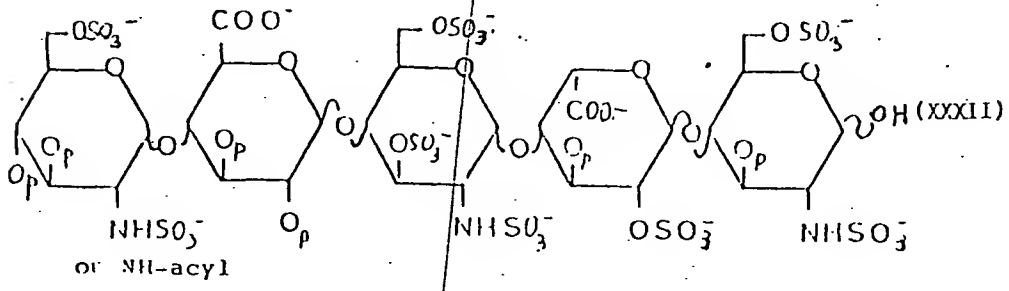
-a tetrasaccharide chain of structure EFGH corresponding to the following formula (XXXI):



(XXXI)

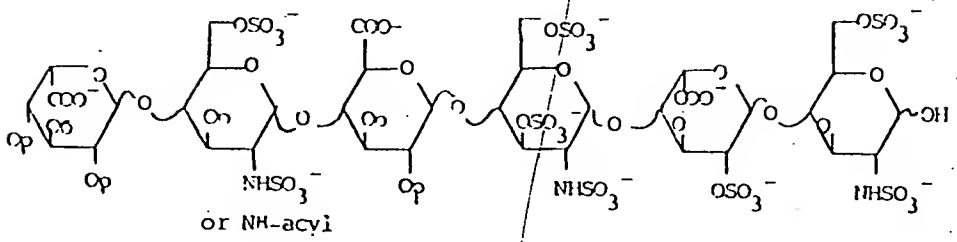
a'

-a pentasaccharide chain, containing or constituted by pentasaccharides of structure DEFGH having formula (XXXII):



(XXXII)

and/or an hexasaccharide chain corresponding to the following formula (XXXIII):



(XXXIII)

35. Oligosaccharides according to claim 34 corresponding to one of the formulae (XXV) to (XXXIII) but containing free -OH groups in place of the -Op groups, and having optionally a portion of the $-OSO_3$ groups replaced by -OH groups.

36. The use of the oligosaccharides according to claim 31,32,33, 34 or 35 as biological reagents.

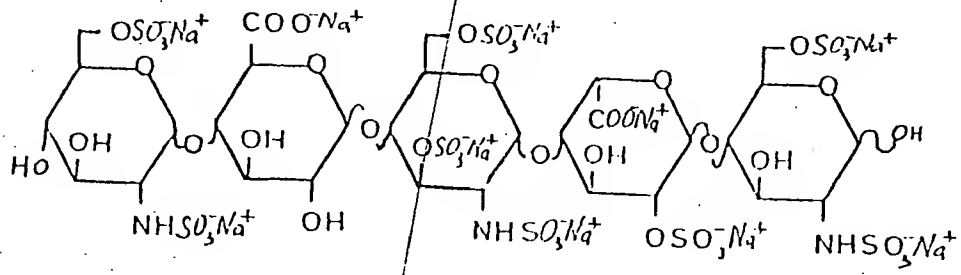
37. Pharmaceutical compositions comprising an effective amount of a biologically active oligosaccharide corresponding to an oligosaccharide according to claim 25,26, 27, 28 or 29 but in which one, several or all the -OH groups

are liberated in the course of synthesis and/or including one or several functional groups, with the exclusion of the disaccharide [2-N-sulphate (or 2-N-acetyl)-6-O-sulphate-D-glucosamine]-methyl-D-glucuronic acid, said functional groups being constituted preferably by esters and occuring more especially in the form of inorganic anions, particularly be sulphate esters or phoisphate esters, these functional groups being borne by one or several primary alcohol and/or secondary alcohol and/or primary amine functions in association with an inert carrier.

a'

38. Pharmaceutical compositions comprising an effective amount of the oligosaccharide of formula (XXXIII) but sulphated and deprotected in association with an inert carrier.

39 Pharmaceutical compositions comprising an effective amount of derivative 50



(50)

in association with an inert carrier.

40. The therapeutic method of controlling thrombosis which comprises the administering to said patient the pharmaceutical composition of claim 39 in an effective amount to control thrombosis.

41. The oligosaccharide of the formula